

Donor lung management: Changing perspectives

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ABSTRACT

Worldwide, lung transplantation has been a therapeutic option for select end-stage lung disease patients who are on optimized medical regimens, but the underlying clinical condition continues to progress. For any successful lung transplantation program, it is important to have a robust donor lung management program. Lungs are commonly affected by the various factors related to trauma or neurogenic in brain stem death donors. This article would focus on the basic protocols to optimize donor lungs which would help in increasing donor pool. It would also elaborate COVID-specific points for donor lung evaluation. This article would also describe the criteria for ideal as well as marginal donor lungs. A comprehensive literature search was performed using PubMed to review various articles related to donor lung management.

KEY WORDS: Donor, lung, management

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INTRODUCTION

Successful lung transplantation program depends on judicious donor lung management as well as robust recipient selection and rehabilitation. This article will highlight various donor lung management related issues, protocols, and novel advances.

EPIDEMIOLOGY

The prevalence of end-stage lung diseases is rising worldwide. Interstitial Lung diseases (ILDs), chronic obstructive pulmonary disease (COPD), cystic as well as noncystic bronchiectasis are the most common respiratory diseases, contributing to the burden of end-stage lung diseases. ILDs comprise mostly commonly idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease-related ILD, sarcoidosis, etc., As

per the ILD Registry of India,^[1] hypersensitivity pneumonitis was the leading ILD (47.3%) followed by connective tissue-associated ILD (13.9%) and IPF (13.7%). Among other end-stage lung diseases, the number of cases of COPD in India increased from 28.1 million (27.0–29.2) in 1990–55.3 million (53.1–57.6) in 2016, an increase in prevalence from 3.3% (3.1–3.4) to 4.2% (4.0–4.4). The disability-adjusted life years per case of COPD and asthma were 1.7 and 2.4 times higher in India than the global average in 2016, respectively; most states had higher rates compared with other locations worldwide at similar levels of sociodemographic index.^[2]

KEY CONCEPTS

End-stage lung diseases usually are progressive, and there is no cure. Lung transplantation has been an option for well-selected patients suffering from progressive end-stage

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lung disease refractory to medical management, thereby improving survival and enhancing quality of life. It has been successful, with better survival worldwide over the last decade or more. The availability of suitable donor organs, resulting in longer waiting times for listed patients with a risk of dying before transplant has been the reason for developing newer techniques to preserve and optimize allografts.

The majority of organs come from patients who are certified as brain dead. Most common causes for brain dead include head trauma, cerebrovascular accidents, including spontaneous intracerebral bleeding and thrombosis, brain tumor, and anoxic, metabolic or toxic brain injury. Lungs from brain-dead donors are sensitive to traumatic situations. Lungs may get injured in the hours before and after brain death resulting from direct trauma, resuscitation manoeuvres, neurogenic edema, aspiration of blood or gastric content, or ventilator-associated trauma and pneumonia, making them unsuitable for transplant.^[3]

The development of ischemia-reperfusion injury, defined as primary graft dysfunction (PGD) by a working group within the Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT)^[4] occurs in the first hours up to 3 days after lung transplantation. PGD is also characterized by low pulmonary compliance, interstitial/alveolar edema, pulmonary infiltrates on chest radiographs, increased pulmonary vascular resistance, intrapulmonary shunt, and acute alveolar injury, as revealed by diffuse alveolar damage on pathology. PGD occurs in various degrees in about 15%–51% of transplant recipients^[5] and leads to 28.3% of deaths in the first 30 days as mentioned by Trulock *et al.*^[6] Rationale donor selection and early management is therefore of importance to get good results and helps in reducing risk for PGD.

The majority of lung transplant programs are conservative in selecting donor lungs, resulting in a wait-list mortality as high as 30%–40%.^[7] The lack of organ donors is significant problem for patients awaiting lung transplantation, because lungs retrieval rate is only 10%–20% of organ donors.^[8] The key to increasing the lung donor pool lies in improving multiorgan brainstem death management, which should be approached as a strategy to avoid losing donors to inadequate protocols, utilising lungs after donation after circulatory death (DCD), using *ex vivo* lung perfusion (EVLPE) and if feasible, using lobar lung living donors.^[7] In India as well, the retrieval rate varies as per state. As per Mohan Foundation,^[9] out of 875 deceased donors in India in 2018, 191 lungs were retrieved. There have been variations in intensive care unit (ICU) protocols for managing donor lung. Implementing an intensive lung donor-treatment protocol is not difficult and hope this article will help in creating awareness. This can help in improving donor organ quality which will reflect in retrieval rate.

Q/A: Who is a standard donor for lungs
Standard donor lung criteria: The International Society for Heart and Lung Transplantation criteria^[10]

Characteristics	Description
Donor PAO ₂ /FIO ₂ ratio	Ratio >400 (FIO ₂ =1.0, PEEP=5-8 cm H ₂ O)
Donor age	<55 years
Smoking history	<20 pack-year
Chest radiograph	Normal chest radiograph without infiltrate
Bronchoscopy	Normal bronchoscopy without significant secretions
Sputum	Absence of organisms on sputum gram stain

It is important to know the variations in these criteria which would be so called extended donor criteria and their impact on allograft survival.

Q/A: What are variations in selection criteria

Age

Increasing donor age is an important risk factor for PGD. However, the average age of donors accepted for transplant has steadily increased. A single-center study has suggested similar 1 year mortality with donors >70-year-old, although larger cohort studies have found increased mortality with donors older than 65 years, suggesting that the utilization of very old donors carries additional risk. A retrospective review also found that the use of donors >50 increased the adjusted risk of death for recipients <60 but not those 60 and above as mentioned in the review by Courtwright and Cantu.^[11]

Note: Donor age is important selection criteria and recipient age should be kept in mind while donor assessment.

Smoking

Smoking is a known risk factor for PGD. However, smoking history is not an absolute contra indication for lung retrieval. Bonser *et al.*^[12] have shown in a cohort study, a prospective registry of 1295 lung transplants that an organ selection policy that uses lungs from donors with positive smoking histories improves overall survival of patients registered for lung transplantation and should be continued. Patients receiving lungs from donors with positive smoking histories had a lower unadjusted hazard of death after registration than did those who remained on the waiting list (0.79, 95% confidence interval [CI] 0.70–0.91). Although lungs from such donors are associated with worse outcomes, the individual probability of survival is greater if they are accepted than if they are declined and the patient chooses to wait for a potential transplant from a donor with a negative smoking history. Taghavi *et al.*^[13] have shown by reviewing UNOS database that double-lung transplantation can be safely performed with lungs from donors with a heavy smoking history (>20 pack years). Freedom from bronchiolitis obliterans syndrome ($P = 0.09$), decrement in FEV1 ($P = 0.12$), peak FEV1 (79.8% vs. 79.0%, $P = 0.51$), and median survival (2043 vs. 1928 days, $P = 0.69$) were not different. On multivariate analysis, such lungs were not associated with death (hazard ratio [HR], 1.003; 95% CI, 0.867–1.161, $P = 0.96$).

Note: As mentioned in ideal donor criteria, it is important to document donor history about smoking status. Smoking history of <20 pack years is ideal although higher pack years might pose a risk factor for long term survival.

Size matching

Total lung capacity (TLC), recipient pathology (obstructive vs. restrictive), and height all are important for appropriate matches between donor and recipient. Predictors of lung size have been used i.e., predicted TLC (pTLC), which estimates lung volumes by using height as an independent variable. This method has been validated. Significant size mismatch, especially undersizing can increase chance of PGD. For double-lung transplants, patients with emphysema should be matched to a donor with a 67%–100% of the recipient's TLC. For pulmonary hypertension and CF patients, the pTLC of the donor may safely reach 120% of the recipient actual TLC. Due to the limitations in TLC that occur in pulmonary fibrosis, the recommendation for donors pTLC is to be within 20% of the halfway point between the recipients actual TLC and pTLC. For SLT (single lung transplant) for fibrotics, the donor pTLC should be within 20% of the recipient's pTLC. It is preferable to slightly oversize if possible and not undersize <80% as mentioned by in the review by Chaney *et al.*^[14] It also mentions that donor ischemia time >7 h and donor age >50 years both together was associated with decreased recipient survival at 2 years.

Graft volume reduction, including peripheral wedge resection, may also be used to improve size-matching, particularly when pTLC >1.6 as documented in review by Courtwright and Cantu.^[11] Size reduced lung transplantation, including split-lung transplantation, lobar transplantation, and peripheral segmental resection, is a reliable procedure providing equal results compared to standard lung transplantation as mentioned by Aigner *et al.*^[15] showing no statistically significant difference between the size-reduced and the standard lung transplantation group with regard to the rate of bronchial healing problems ($n = 3/9$; $P = 0.62$) or the rate of revision due to postoperative bleeding ($n = 6/15$; $P = 0.77$). The 3-month survival rate was 86.3% in the size-reduced 92.0% in the standard group ($P = 0.09$).

Note: Size matching is an important step in lung transplantation and would help minimize intra-operative as well postoperative complications.

PaO₂/FiO₂ ratios

Gabbay *et al.*^[16] have shown that therapeutic manipulation of donors helps to improve their gas exchange resulting in better utilization of marginal lungs. Management involved antibiotic therapy in suspected sepsis and physiotherapy, judicious fluid balance, increasing tidal volume and PEEP (Positive End -Expiratory Pressure), bronchial toilet to remove secretions and reduce atelectasis. In 20 donors (out of 59 [34%] with an initial PaO₂/FI O₂ ratio of <300 mm Hg), there was an improvement in gas exchange to a PaO₂/FI O₂ ratio of >300 mg. Zafar *et al.*^[17] in the review study of UNOS data of 12,045 patients showed no difference in graft survival with differing donor PaO₂(2) s, irrespective of whether patients had a single or double LTx. Even though P/F ratio is important, if it is <300, does not imply no retrieval. Adequate

comprehensive lung management would be required for optimizing the ratio.

Note: Maintaining ideal P/F ratio and optimizing it in cases where it is inadequate should be an important goal in donor lung management.

Donor lung infection

No pulmonary infection is an ideal criteria for donor lung. Routine prophylaxis of every recipient with broad spectrum antimicrobials would help maintain donor lung. Weill *et al.*^[18] demonstrated that of the 43 patients with a positive donor gram stain (DGS), 5 (12%) developed pneumonia, compared to 9 of 44 (20%) with a negative DGS ($P = 0.26$). The mean postoperative P/F ratio (315 ± 47 with a positive DGS, $P = 0.3$) and length of mechanical ventilation (2 days in each group) did not differ significantly between the negative and positive DGS groups, thus concluding that DGS does not predict the development of early postoperative pneumonia and does not affect oxygenation or duration of mechanical ventilation. Furthermore, the presence of donor organisms does not predict posttransplant pneumonia (PTP) as mentioned by Bonde *et al.*^[19] In this review of 64 donors, the donor organisms had a sensitivity of 0.75 with a low specificity of 0.04 and were negatively correlated with development of PTP. Analysis by Mattner *et al.*^[20] revealed that in only 11 out of 282 transplants (3.9%, CI [95%] 2.0%–6.9%), organisms of posttransplantees and of contamination of the donor organ were of the same species indicating that posttransplant infections due to donor related were rare under the condition of adequate preoperative antibiotic prophylaxis and aseptic organ retrieval despite high donor contamination.

Note: Bronchoscopic assessment of donor lung is important and BAL should be collected for evaluation.

Length of ventilation and graft ischemia time

There is no indication that donors should be excluded solely on the basis of the length of mechanical ventilation. Most transplant centers prefer an ischemic time limited to 4–6 h.^[3]

Donor lung radiology

Donor lung radiological assessment is an important part of decision making in lung retrieval. McCowin *et al.*^[21] have shown that initial lung densities were present in 37% of lungs; there were bilateral infiltrates in 25% of cases. During evaluation, 38% of right lungs and 28% of left lungs improved radiographically. Up to 51% of lungs with initial infiltrates resolved completely. More than 33% of proposed organ donors initially have lung infiltrates, with >33% showing improvement or resolution.

Diffuse bilateral lung infiltrates would require also ruling out infection, especially in a patient with high temperature and purulent secretions.

Other reason for infiltrates is likely aspirations or pulmonary oedema which could be neurogenic or

fluid overload related wherein for latter, diuretics with recruitment strategy would play an important role in improving those radiological infiltrates thus improving P/F ratios.

Rational Donor Lung Management can lead to significant Radiological improvement [Figures 1 and 2] in some cases. Lung parameters like Compliance, Tidal Volume, etc also tend to improve.

Note: Doing HRCT Thorax whenever feasible should be done for better radiological assessment.

ABO compatibility

Lung transplantation would require ABO compatibility to prevent hyperacute rejection, leading to immediate graft failure and death.

Marginal donor lung

Marginal donors are commonly encountered in an active lung transplant program. The Toronto group by Pierre *et al.*^[22] have stated that the increased mortality risk in the patients by using lungs from marginal donors was justified, as waiting time is long and thus mortality on the waiting list is high in their transplant center. Extended donor criteria used were donor age >55 years, smoking >20 pack years, infiltrates on cxr, paO₂ <300 mm Hg, and purulent bronchoscopic findings. Early 30-day mortality was 6.2% in the standard donor group and increased to 17.5% in the extended donor group. Unilateral infiltrates, basal or dependent atelectasis, and mucoid secretions suctioned out completely almost always result in good graft function.

Donor lung management strategies

Ventilation

A 2010 trial by Mascia *et al.*^[23] in a randomized controlled study, lung protective ventilatory protocol showed an increase in donor eligibility using this protective strategy compared with the conventional strategy (95% vs. 54%), and an increase in the number of lungs retrieved

for transplantation (54% vs. 27%). Ventilation with conventional tidal volume 10–12 ml/kg may overstretch lungs in the presence of markedly decreased lung compliance, which occurs in pts with lung injury.

Lung protective ventilation strategy includes tidal volume of 6–8 ml/kg IBW, plateau pressure <30 cmH₂O, adequate PEEP 8–10 cm H₂O, FiO₂ <0.5 to keep SpO₂ 92%–95%.

Note: Ventilatory strategy which helps better lung recruitment which eventually improves P/F ratio is important for better graft survival.

Hormone replacement

Hormone therapy after brain death in combination with a central venous pressure <10 mmHg significantly improved utilization of the heart and lungs for transplant without affecting other organ systems.^[24] The recommended replacements are:

- Vasopressin 1 U bolus followed by an infusion of 0.5–4.0 U/h (desmopressin intranasally has a selective action on the V₂ receptors and a half-life varying from 6 to 20 h) (Diabetes insipidus)
- Methylprednisolone 15 mg/kg immediately after the diagnosis of brain death and 24th hourly thereafter (Adrenal Insufficiency)
- Insulin 10 U in 50% dextrose followed by an infusion to maintain blood glucose between 80 and 150 mg (hyperglycemia)
- Thyroxine (T₄) 20 mcg bolus followed by infusions of 10 mcg/h. Tri-iodothyronine (T₃) given as a 4-mcg bolus followed by an infusion of 3 mcg/h. T₄ improves hemodynamics and prevents cardiovascular collapse in hemodynamically unstable organ donors (thyroid deficiency).

Literature

Hormonal resuscitation therapy with methylprednisolone, vasopressin, and thyroid hormone has been associated with brain-dead donor stabilization and a better retrieval rate.



Figure 1: Donor Lung CXR: Before optimisation (Original)

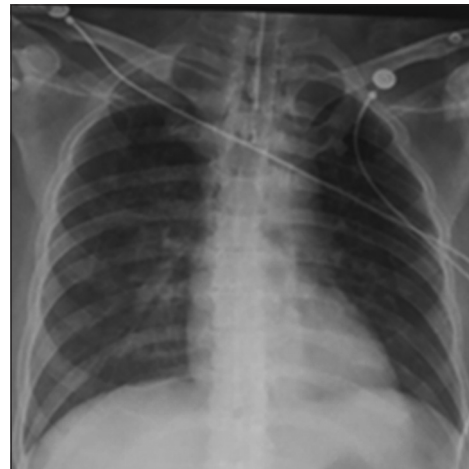


Figure 2: Donor lung CXR: After Optimisation (Original)

In an analysis by Salim *et al.*^[25] on 123 multi-organ donors, compared with donors who did not receive thyroid hormone T4, those that did were similar in age (32 ± 14 vs. 38 ± 21 , $P = 0.148$), had more organs donated (3.9 ± 1.7 vs. 3.2 ± 1.7 , $P = 0.048$), and had no differences in brain-death related complications. Despite the severe hemodynamic instability in the T (4) group, the number of organs harvested from this group was significantly more than in patients who did not receive T4.

In a study by Abdelnour and Rieke^[26] showed that standardization of hormonal resuscitation therapy receiving thyroid hormone, in combination with a CVP <10 mm Hg, significantly increases the utilization of hearts and lungs for transplantation, without negatively impacting other organ systems. When a final CVP <10 mm Hg was achieved, 44% more hearts, 95% more lungs and 13% more kidneys were able to be transplanted.

In a review by Callahan *et al.*^[27] including 12,322 donors, it was demonstrated that there was a significant increase in high yield (≥ 4 organs) (51.0% vs. 39.3%, <0.001), mean number of organs (3.75 vs. 3.33, <0.001), and rate of successful lung recovery (26.3% vs. 20.5%, <0.001) with AVP. Lung function was preserved to a greater degree in donors receiving AVP. Adjusting the significant factors, AVP was independently associated with lung procurement (1.220 [1.114–1.336], <0.001).

Note: Hormone replacement becomes an important part of Donor lung management as brain death leads to endocrinal/hormonal imbalance which needs to be corrected.

Intensive care unit protocols

Miñambres *et al.*^[6] demonstrated the utility of restrictive fluid balance with a goal EVLW index <10 mL/kg, CVP <8 mmHg, lung recruitment maneuvers, mechanical ventilation with tidal volume of 6–8 mL/kg and PEEP 8–10 cmH₂O, appropriate maneuvers to avoid aspiration, bronchoscopies with BALs, the use of methylprednisolone (15 mg/kg) and the semi-lateral decubitus position. Of the 45 lung donors, 15 (33.3%) had PaO₂/FIO₂ <300 mm Hg at the beginning of the protocol, which finally increased to >300 mm Hg. In the protocol period, early survival (30 days) in recipients who received graft lungs from donors with constant PaO₂/FIO₂ > 300 mm Hg ($n = 26$) was similar to that of recipients from donors with PaO₂/FIO₂ < 300 mm Hg at the beginning of management ($n = 15$): 84.1% vs 93.3% ($P = 0.382$), respectively. No differences were observed in retrieval rate for the other organs in lung donors. The number of annual potential lung donors, lung donors and lung donors utilized doubled over the protocol period Lung donation rate in the prospective group was 27.3%, more than twice that of the historical group 13%; ($p < 0.001$). If only donors ≤ 70 years old were considered, the lung donor rate increased from 18.1% to 39.5% ($p < 0.001$). Alveolar recruitment protocol was controlled ventilation (plateau pressure limit of 35 mm Hg) with PEEP of 18–20

cm H₂O for 1 minute and decreasing by 2 cm H₂O each minute; then increasing 50% tidal volumes for 10 breaths. Recruitment maneuvers once per hour and after any disconnection from the ventilator

In a prospective study on 219 lung donors, Gabbay *et al.*^[16] demonstrated that the application of the bundle (appropriate antibiotic therapy, physiotherapy, increased tidal volumes and PEEP and bronchial toilet together with a strict fluid management) to 59 suboptimal donors with PaO₂/FiO₂ ratio below 300 mmHg, made 20 lungs, otherwise rejected, suitable for transplantation

The San Antonio Lung Transplant (SALT) program, implemented by Angel *et al.*^[28] consists in maneuvers of active alveolar recruitment with inspiratory pressure (Pinsp) of 25 cmH₂O and PEEP of 15 cmH₂O for 2 h, minimize crystalloid use and administration of diuretics, bed elevation at 30°, endotracheal cuff pressure at 25 cmH₂O to reduce the risk of aspiration and bronchoscopy with bilateral bronchoalveolar lavage. The mean final PaO₂/FiO₂ of the actual lung donors was significantly better during the SALT period (PaO₂/FiO₂, 463) than during the pre-SALT period (PaO₂/FiO₂, 416; $P = 0.02$). The rate of bilateral lung transplantation increased from 19% during the pre-SALT period to 37% during the SALT period ($P = 0.02$). The 30-d survival rate (81% pre-SALT; 99% SALT; $P = 0.005$) and the 1-year survival rate (76% pre-SALT; 85% SALT; $P = 0.14$) improved after the implementation of the SALT protocol

Some common physiological derangements in brain dead patients are hypothermia, hypotension, diabetes insipidus, DIC, arrhythmias, and pulmonary edema. Goals as suggested by McKeown *et al.*^[29] for active donor management are as follows: (1) heart rate: 60–120 beats per min, (2) Arterial pressure systolic more than 100 mm Hg and mean pressure more than 70 mm Hg, (3) CVP 6–10 mm Hg, (4) Urine output 0.5–3.0 ml/kg/h, (5) Electrolytes Sr Na 130–150 mmol/l and normal potassium, calcium, magnesium, and phosphate, (6) Active warming to maintain temperature more than 35°C before and during retrieval, (7) Avoiding excessive fluid loading in donor management has now been consistently shown to increase the numbers of transplantable lungs. If vasopressor drug is required, vasopressin may reduce catecholamine requirements. High doses of catecholamines, i.e. Norepinephrine >0.05 µg/kg.min should be avoided if possible to prevent increased cardiac graft dysfunction (8) Balanced salt solutions may help prevent hyperchloremic acidosis if large volume of crystalloids required. Also high doses of starch based colloids should be avoided as suggested by McKeown *et al.*^[29]

Recent Literature: As per recent ISHLT statement^[10], (a) Assess ECG, CXR, ABG, urgent sputum trap -Gram stain, AFB stain, Fungi (b) Optimise Volume status: Target CVP 6-10 mm Hg (c) Adjust Vasopressors: To keep MAP above 60 mm Hg (target Vasopressin dose < 2.4 Units/hr or Dopamine < 10 mcg/kg/min (d) Protective Ventilation Strategies (e)

Correct Acidosis (f) Correct Hypoxaemia: Target PaO₂ 80-100 mmHg, SaO₂ > 95% (g) Control Hyperglycemia (4-10 mmol/L) (h) Hormonal Resuscitation (If on Dopamine, start Vasopressin infusion 2.4 U/hr and If on Vasopressin, start Dopamine at 4 µg/kg/min) (i) In donors with decreased pre-load, crystalloid solutions (0.9% sodium chloride or Ringer's lactate) are the preferred choices for fluid repletion and maintenance. Dextrose containing fluids or hypotonic solutions, such as 0.45% sodium chloride, may be used in patients with hyponatremia (Serum Na⁺ > 145 mmol/liter) after correction of hypovolemia. (j) Careful fluid management avoids massive crystalloid infusion, which has a detrimental effect on arterial oxygenation. Surgeons should evaluate the lungs for pulmonary edema at the donor hospital. (k) Bronchoscopy is performed early for an accurate evaluation of bronchitis, aspiration, obtaining sputum samples, and bronchoalveolar lavage if an infection is suspected, and to clear stagnant secretions that may cause atelectasis or inhalation injury.

Note: Various ICU protocols are implied with common goal of optimizing Donor as a whole to make multi-organs viable for donation.

Reasons to decline lungs at procurement centre:^[10] (a) Inability to recruit (b) Unacceptable PaO₂:FiO₂ (P/F) ratio (c) Unanticipated confirmation of primary or non-primary malignancy (d) Severe trauma not appreciated on CT (e) New data on non-compatibility (f) Demise of original recipient during transit (g) Withdrawal of consent from the donor's decision maker

Lung preservation at procurement and in transit

Nguyen *et al.*^[30] have mentioned about the standard practice for lung preservation. Perfadex solution is an extracellular dextran-based, low potassium solution that reduces interstitial edema and maintains epithelial cell integrity. On a cellular level, high potassium preservation solutions resulted in decreased membrane potential hyperpolarization, more depolarization of the resting membrane potential, and decreased hyperpolarization-associated relaxation of the pulmonary arterioles as compared to extracellular based low-potassium solution (Perfadex). Prior to cross clamping of the aorta, 500 µg of prostaglandin are injected into the pulmonary trunk. Prostaglandin is a potent pulmonary vasodilator that counteracts the pulmonary vasoconstriction with cold pulmoplegia and improves perfusion throughout the lungs. Pulmoplegia flush is then initiated by gravity dependent flow. A total of 4–5 l of Perfadex is administered antegrade, sufficient flush is evident when the left atrial effluent becomes clear colored. Additional Perfadex solution is administered in a retrograde fashion through each of the pulmonary veins (~500 mL per pulmonary vein). Pulmonary blood clots (emboli) are frequently seen in the pulmonary artery effluent, manual palpation of the respective lobe encourages egress of these clots during retrograde flush of the pulmonary veins.

Advantages of retrograde flush relate to the improved distribution of preservation solution to include flushing of the bronchial arteries with improved surfactant function. The donor lungs are then placed in a sterile plastic bag containing cold Perfadex solution and sealed.

Munshi *et al.*^[31] has also elaborated about lung preservation which comprises of following principles i.e. Extracellular solution consisting of dextran-40, glucose, and low potassium; antegrade and retrograde flushing at 60 mL/kg and 30 cm height, storage temperature 4°C–8°C, inflation to 50% of TLC, fraction of inspired oxygen 50%, pharmacological additives like prostaglandin E₁, heparin, glucocorticoids, cold ischaemic times generally <8 h, normothermic EVLP based on lung assessment and therapeutics.

Thus, lung preservation goes a long way in deciding graft survival and it is imperative for retrieval team to know techniques of antegrade and retrograde flushing, transport care, ice box preparations, etc., till the organ reaches OT table for transplantation. These static cold storage/lung preservation techniques help in allograft preservation by decreasing cellular metabolism, cytoprotection by anti-oxidant properties, preventing thrombosis by flushing, minimising lung injury during period of ischemia, etc.

Ex vivo perfusion and preservation

EVLP is a technique used to evaluate and screen compromised donor lungs with potential for recovery. This technique has been already used in lung transplantation centres across the world. EVLP can restore the circulation and ventilation of the *ex vivo* lung. At an ambient temperature of 37°C, a membrane oxygenator is used to simulate oxygen consumption in the body via deoxygenation and maintain the physiological state of lungs with specific perfusate and ventilation. The Steen solution is currently the only Food and Drug Administration-approved EVLP perfusate for clinical use. The ventilation gas in the lung membrane consists of N₂ (86%), CO₂ (8%), and O₂ (6%). The hypoxic gas mixture removes the oxygen in the circuit to simulate oxygen consumption in the body. The EVLP system includes a ventilator, an endotracheal tube, perfusate and a fluid circuit, a reservoir, an oxygenator, a pump, and a thermostat as elaborated by Pan *et al.*^[32] EVLP is currently used mainly to evaluate certain high-risk donor lungs. It is mainly indicated for: (I) an oxygenation index <300 mmHg; (II) pulmonary edema as indicated by the last chest X-ray; (III) collapse or poor expansion of a donor lung during harvest; (IV) blood transfusion >10 U; and (V) lungs from donors with cardiac death. EVLP is not suitable in cases of apparent pneumonia, severe mechanical lung injury (including multiple lobar injury), or significant aspiration of gastric contents. After EVLP, a donor lung is considered eligible for transplant if the oxygenation index reaches 400 mmHg after 4–6 h of EVLP; chest X-ray findings are stable or improved; and pulmonary artery pressure, airway pressure, and lung compliance are stable or improved. A reconditioned donor lung is

considered ineligible for transplant if the oxygenation index is <400 mmHg; pulmonary arterial pressure, airway pressure, or lung compliance worsens by $\geq 15\%$ from baseline; and chest X-ray shows worsening signs as mentioned in the review by Xufeng Pan *et al.*^[32]

Possoz *et al.*^[33] has mentioned about four commercial systems that are available on the market nowadays: OCSTM Lung (Transmedics, Andover, Massachusetts, USA), Lung Assist™ (Organ Assist, Groningen, The Netherlands), XPSTM and LSTM (XVIVO, Göteborg, Sweden). There are three EVLP protocols currently used worldwide: Toronto, Lund, and Organ Care System™ (OCS, Transmedics, Andover, MA, USA). These protocols differ by the perfusate used, target flow, pulmonary arterial pressure, left atrial pressure, and ventilatory settings.

Zhang *et al.*^[34] have shown that transplantation of the previously discarded lungs recovered by EVLP leads to equal outcomes compared to conventional LTx methods. Three-year survival was 78% (7/9) (the EVLP group) versus 83% (15/18) (the N-EVLP group).

Every Transplant program should have a preservation plan which includes the donor-management ICU team, the retrieval team, and EVLP team if available. The area of EVLP is encouraging and will be a ray of hope to increase the donor pool.

DONATION AFTER CIRCULATORY DEATH

DCD donors are defined as when organs are removed from donors after cardiac arrest. Selective use of EVLP is a part of the DCD Program in most centers. Broadly, DCD donors are divided into controlled and uncontrolled donors (modified Maastricht classification) as mentioned in the review by Inci.^[35] Van Raemdonck *et al.*^[36] in their study cohort of 11, 516 lung transplant pts with 5-year follow-up has shown similar excellent long-term survival in DCD-III and Donation after Brain Death (DBD) lung donor recipients in 23 experienced centers. On multivariable analysis, transplant diagnosis (bronchiectasis versus pulmonary fibrosis; HR: 1.48 [1.21, 1.80]; and other indications vs. pulmonary fibrosis: HR 1.22 [1.09, 1.37]), procedure type ([single lung versus bilateral and double lung]: HR 1.21 [1.11, 1.32]), and trans-plant era (2003–2009 vs. 2010–June 2016: HR 1.18 [1.10, 1.27]) were all independently associated with survival ($P < 0.001$). More importantly, donor type (DCD-III vs. DBD) was not (HR 1.04 [0.90, 1.19]; $P = 0.61$). Five-year survival rates were comparable (63% vs. 61%, $P = 0.72$).

COVID PANDEMIC AND LUNG TRANSPLANT PROGRAM

WHO declared COVID-19 infection (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), a novel coronavirus infection “a pandemic” on 12 March 2020. The COVID-19 infection can cause mild to severe illness with more

severity in adults 65 years and older and people of any age with serious underlying medical problems. As per ISHLT statement,^[37] recommend pre-transplant COVID-19 symptom donor assessment. Donor currently suffering from a clinical syndrome compatible with COVID-19, regardless of known exposure within the past 10 days and negative PCR test results, should be avoided (unless alternative diagnosis is made). Additionally, recommend testing for SARS-CoV-2 by nasopharyngeal/ oropharyngeal swab, sputum/ tracheal aspirate, or bronchoalveolar lavage (BAL) less than 72 hours before organ donation. All should be tested for SARS-CoV-2 infection by PCR-based method for SARS-CoV-2. It is strongly recommended to do a deep respiratory specimen (bronchial wash, BAL, mini-BAL, or tracheal aspirate) for SARS-CoV-2 RNA for all lung donors. It recommended to avoid transplantation from PCR + donors. A thoracic computed tomography (CT) scan may show signs of SARS-CoV-2 infection even before the development of symptoms or positive PCR and should be considered for donor and recipient assessment. If CT imaging is suggestive of a viral pneumonitis, it is recommended to decline the donor offer. As per previous ISHLT statement,^[38] the center should have a discussion of risk-benefit with the recipient regarding transplantation during the ongoing pandemic. Appropriate PPE should be available for the procurement team on site either provided by the local organ procurement organization, the donor hospital, or carried by the procurement team according to their institutional guidelines. N-95 masks (or equivalent) should be worn by all team members in the operating room during lung retrieval and lung transplantation; face shield is suggested as well. It is recommended to avoid donor bronchoscopies in the operating room; if performed, only the bronchoscopist should be in the room with airborne precautions. Negative pressure operating room should be used for lung surgical procedures.

2 Updated Donor Clinical Scenarios:^[37]

- A) Exposure to confirmed or suspected case of COVID-19 within past 10 days: Organ may be considered for cardiothoracic transplant if: Donor has been asymptomatic and >7 days since exposure and at least one negative *SARS-CoV-2 PCR test and CT chest negative for pulmonary infection and potential candidate with high risk of mortality without organ transplantation *Deep respiratory specimen recommended for lung donors
- B) Donor with prior confirmed COVID-19: May be considered for transplant if: Clinical resolution of symptoms due to COVID-19 and >21 days from onset of symptoms in an immunocompetent donor and no significant pulmonary disease due to COVID-19 (for e.g. required intubation) and at least one negative *SARS-CoV-2 PCR and CT scan of the chest negative for evidence of pulmonary infection/chronic lung injury A

lower respiratory sample for SARS-CoV-2 PCR is strongly recommended for all lung donors

- C) Antigen test is not acceptable for donor evaluation. COVID-19 vaccination status of the donor does not alter these recommendations

With COVID times, donor and recipient management is going to be modified to sustain lung transplant programs, especially when the virus continues to affect millions of lungs with newer indications of lung transplant arising in the form of post-COVID ARDS fibrotic end-stage lung disease.

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Conflicts of interest

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